

Initiation and Titration of Insulin in Diabetes Mellitus Type 2

Greg Doelle MD, MS

April 6, 2016

Disclosure

I have no actual or potential conflicts of interest in relation to the content of this lecture.

Objectives

- Timing of insulin administration in type 2 diabetes
 - Basal insulin
 - Bolus insulin
 - Biphasic insulin
- Insulin choice
 - Insulin analogs
 - Human insulin
- Patient preference and values

Glycemic Recommendations for Nonpregnant Adults with Diabetes

The first step in the treatment of patients with type 2 diabetes is setting glycemic targets

The current standard of care involves individualizing these targets on the basis of patient characteristics

Ultimately, the goal of any treatment should be to provide the patient with the greatest possible improvement in both short- and long-term quality of life

Glycemic Recommendations for Nonpregnant Adults with Diabetes

A1C	<7.0%
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Preprandial capillary plasma glucose	80–130 mg/dL
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Peak postprandial capillary plasma glucose	<180 mg/dL
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Glycemic Recommendations for Nonpregnant Adults with Diabetes

Goals should be individualized based on

- Duration of diabetes

- Age/life expectancy

- Comorbid conditions

- Known CVD or advanced microvascular complications

- Hypoglycemia unawareness

- Individual patient considerations

 - psychologic

 - economic

 - support systems

 - social functioning

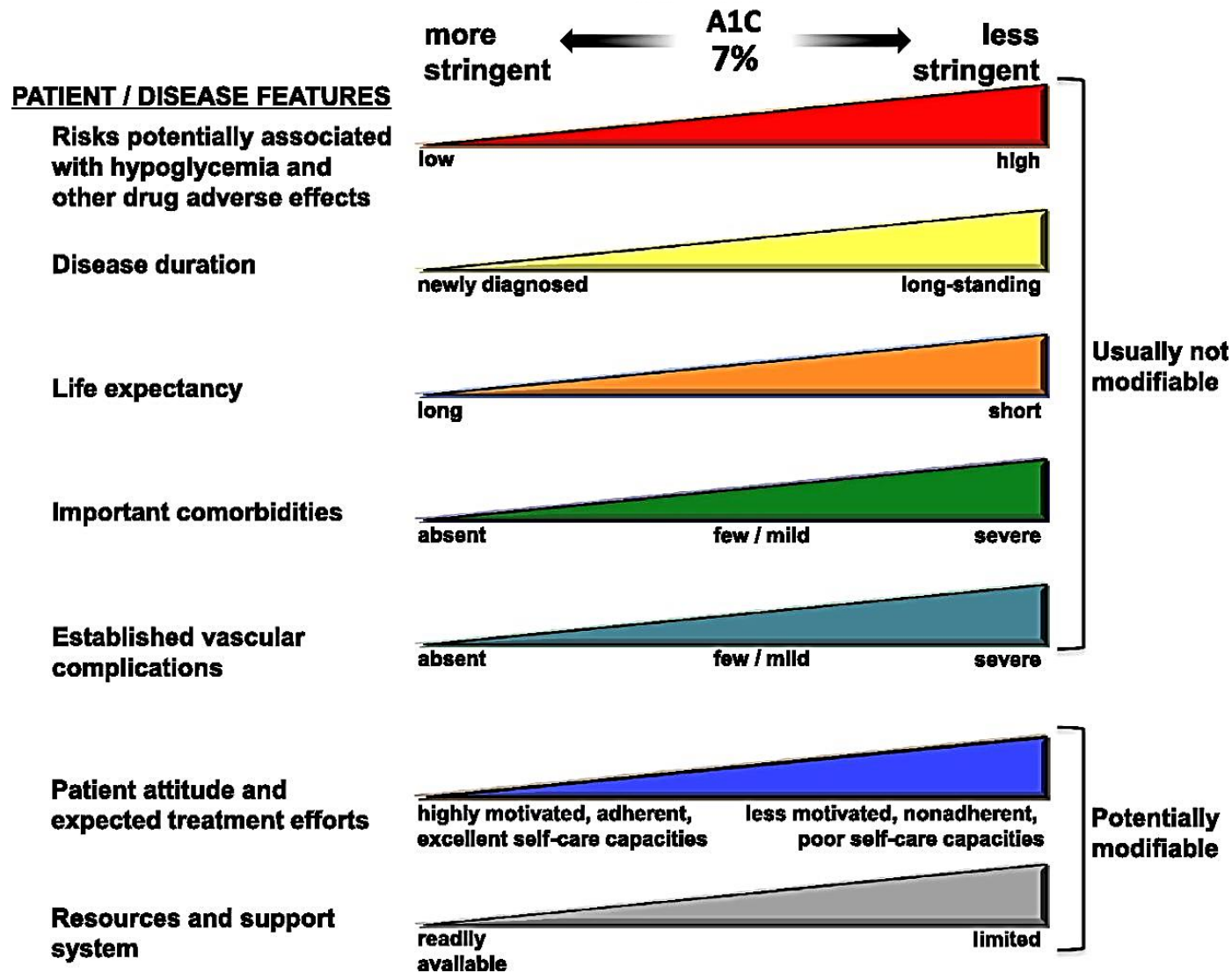
Glycemic Recommendations for Nonpregnant Adults with Diabetes

Less stringent A1C goals (such as <8%) may be appropriate for patients with

History of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions

Those with longstanding diabetes in whom the general goal is difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin

Approach to the Management of Hyperglycemia



Recommendations: Pharmacological Therapy For Type 2 Diabetes

Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes

If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the A1C target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or insulin

In patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C, consider insulin therapy (with or without additional agents)

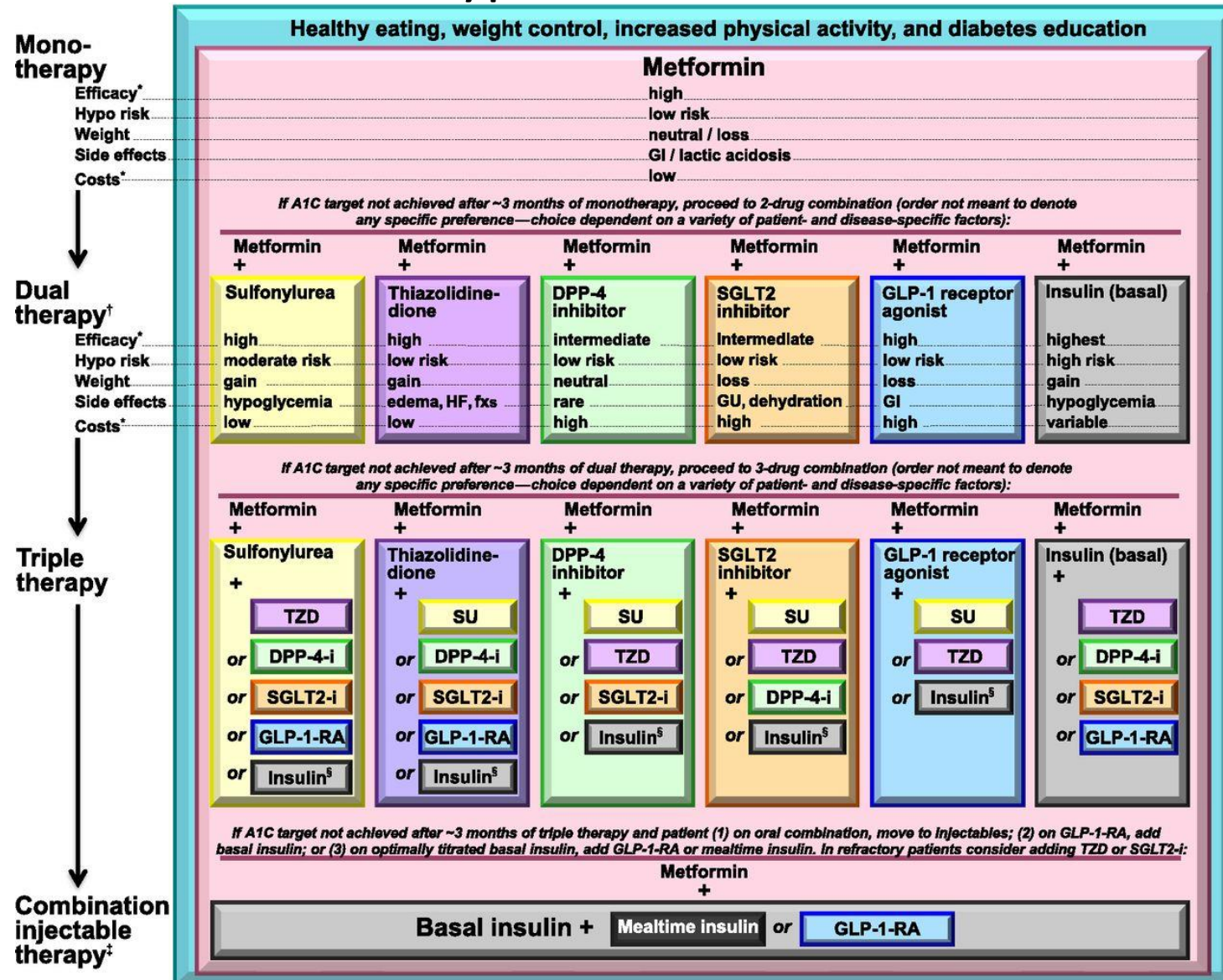
Recommendations: Therapy for Type 2 Diabetes

A patient-centered approach should be used to guide choice of pharmacological agents

Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences

Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes

Antihyperglycemic Therapy in Type 2 Diabetes



Diabetes Care 2016;39(1);S61

Insulin Therapy in Type 2 Diabetes: Lessons Learned from Outcome Studies

- UKPDS
 - Intensive glycemic control in *newly* diagnosed patients led to a 25% reduction in overall microvascular complications
- UKPDS
 - Patients randomized to intensive therapy showed a significant reduction for any diabetes related endpoint and for MI at 10 years
- ADVANCE, VADT
 - Intensive glycemic control yielded no benefit in cardiovascular disease outcomes
- ACCORD
 - Intensive glycemic control led to a significant increase in mortality including an increase in cardiovascular mortality

Insulin Therapy in Type 2 Diabetes: Lessons Learned from Clinical Trials

- Patients can successfully titrate basal insulin to treatment targets
- Basal insulin *analogs* are associated with fewer episodes of nocturnal hypoglycemia than NPH
- Supplementation with basal insulin is associated with improvements in both first and second phase prandial insulin secretion
- Basal insulin compared to prandial or biphasic insulin initiation is associated with fewer hypoglycemic episodes and less weight gain
- *After 3 years, the majority (> 80%) of patients started on basal insulin are also taking prandial insulin*

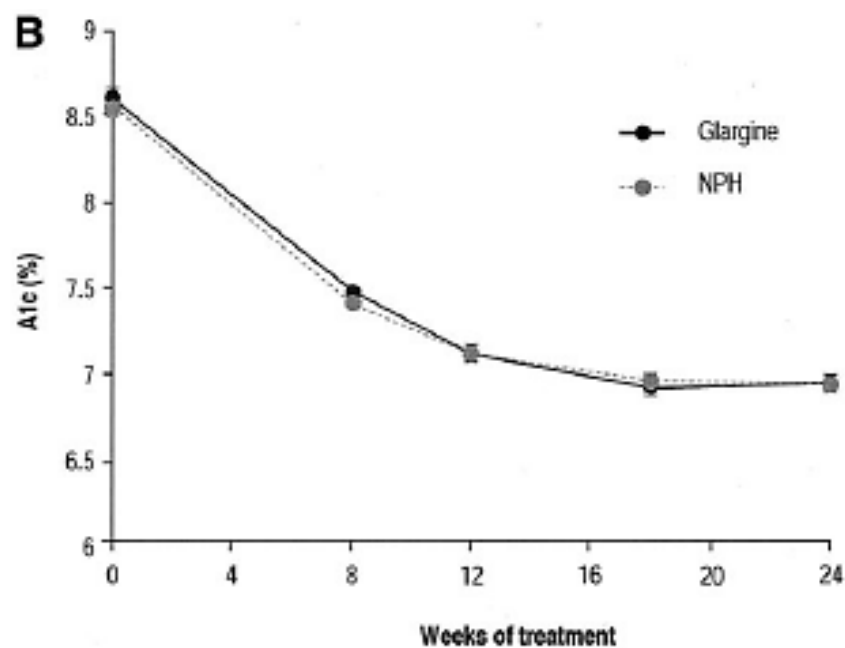
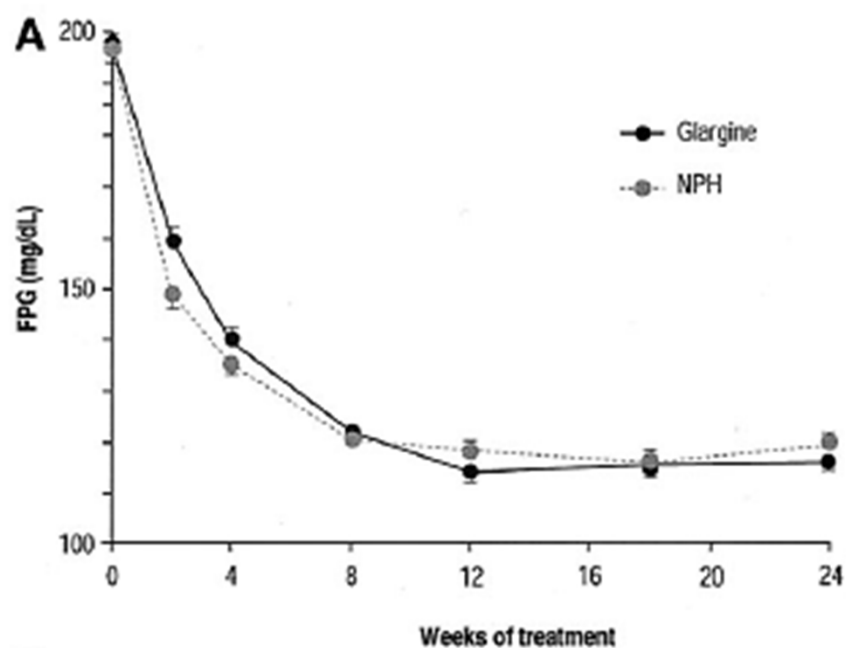
Insulin Therapy in Type 2 Diabetes

- **Basal:** Simple to use, low injection frequency, well tolerated. Establishes patient confidence in insulin. Relatively low risk of hypoglycemia. May facilitate “beta cell rest” leading to some recovery of prandial insulin release.
- **Prandial:** Demanding, with need for carbohydrate counting and multiple injections. Higher hypoglycemia risk.
- **Premix (biphasic):** Simple way of supplementing both basal and prandial insulin. Fixed dose ratio, titration not straightforward.

When to Initiate Insulin Therapy in Type 2 Diabetes

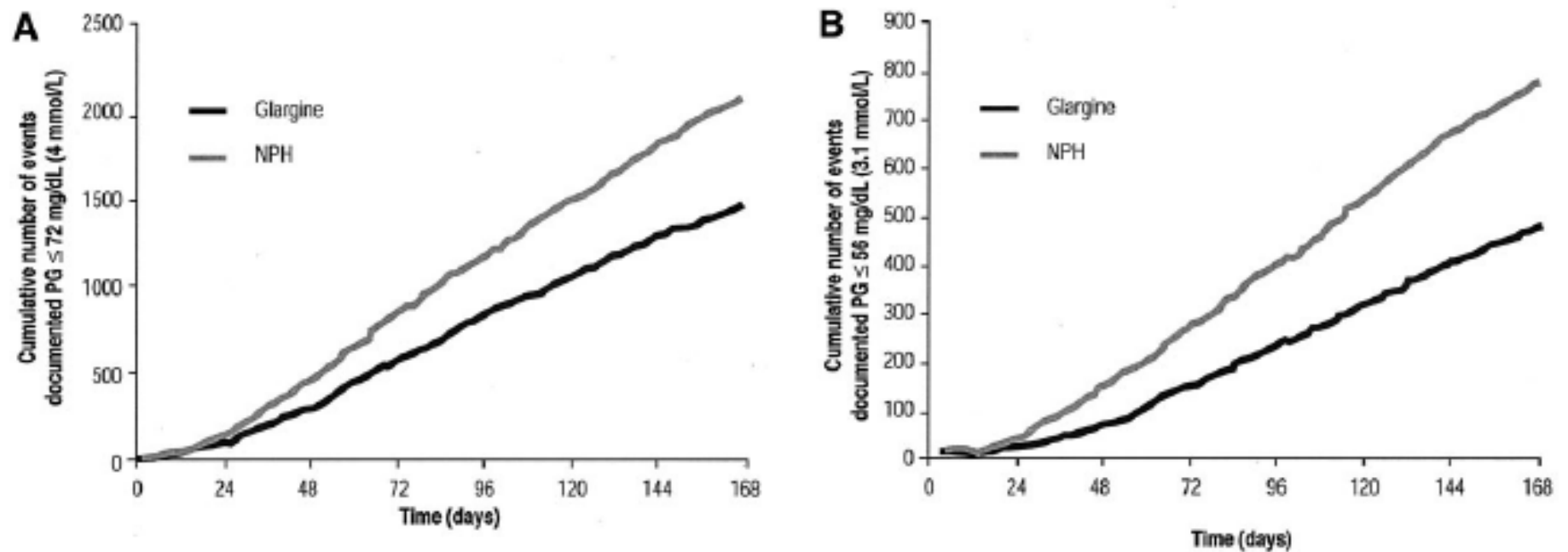
- **Entry** hemoglobin A1c
 - > 9%
 - Basal insulin
 - TDD 0.2-0.3 units/kg
 - > 11%
 - Basal-bolus insulin (or biphasic insulin)
 - TDD 0.3-0.5 units/kg
- **On-treatment** hemoglobin A1c
 - < 8%
 - Basal insulin
 - TDD 0.1-0.2 units/kg
 - > 8%
 - Basal insulin
 - TDD 0.2-0.3 units/kg

Fasting Glucose and HbA1c Values Following Introduction of Basal Insulin



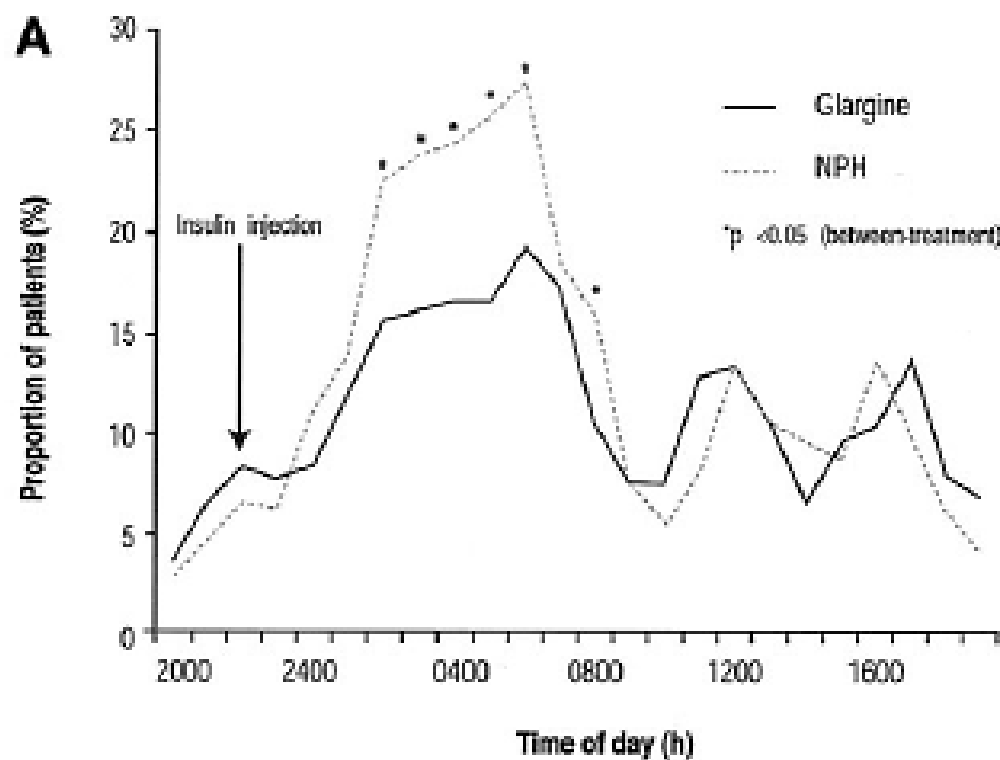
Diabetes Care 2003;26;3080

Cumulative Hypoglycemic Events Following Introduction of Basal Insulin



Diabetes Care 2003;26;3080

Distribution of Hypoglycemia Following Introduction of Basal Insulin

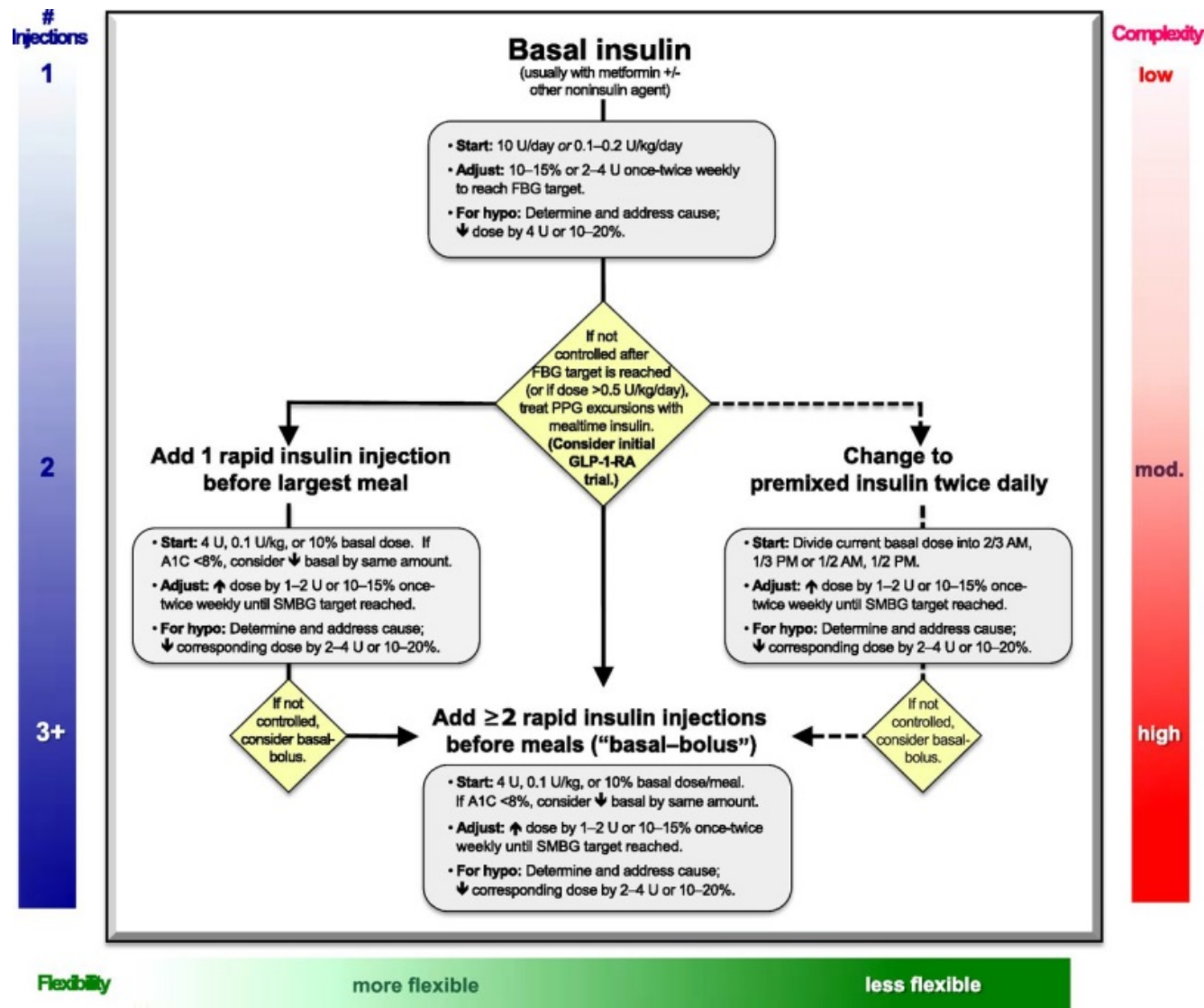


Diabetes Care 2003;26;3080

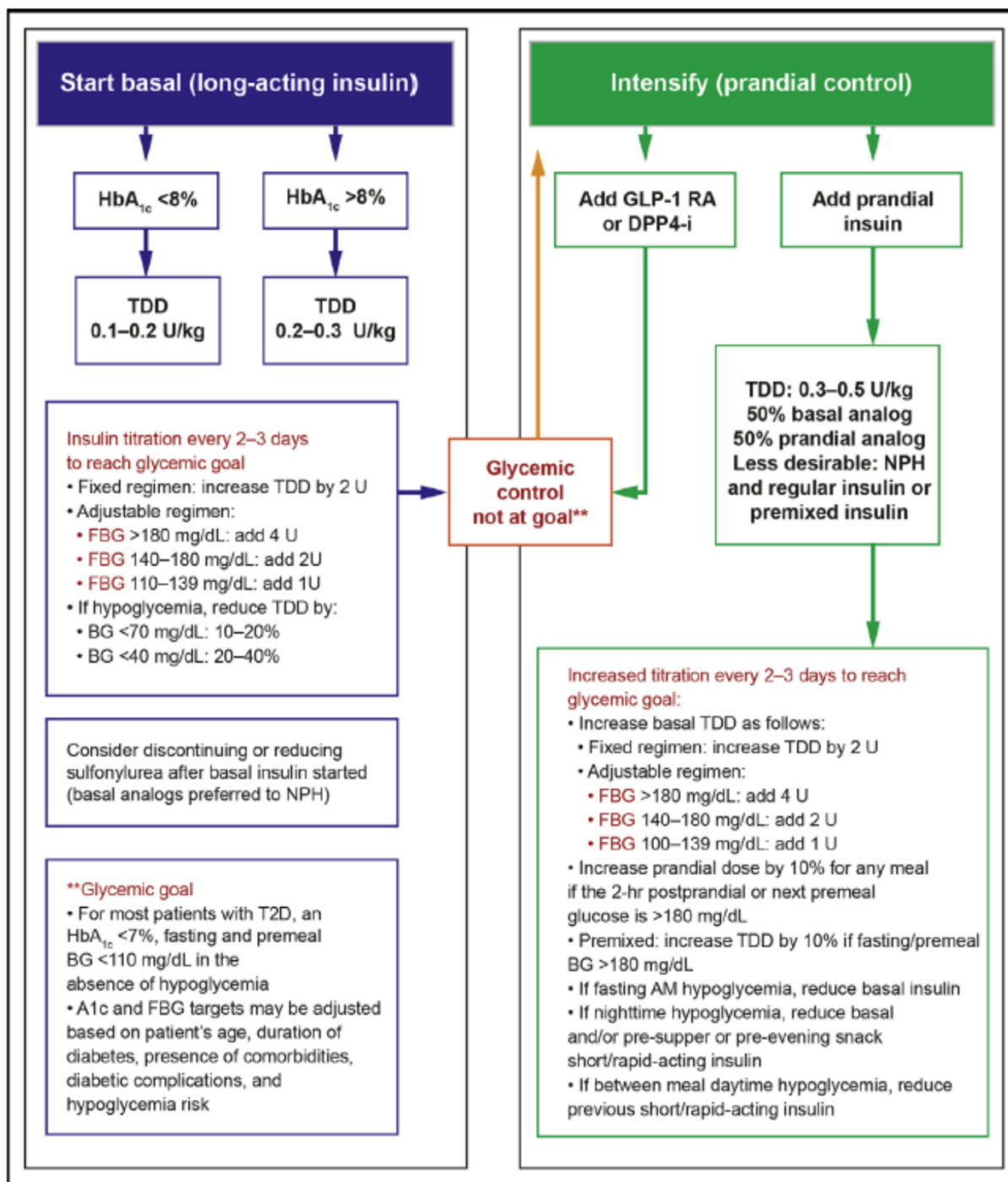
Basal Insulin

- Usually in combination with metformin +/- other non-insulin agent
- Total daily dose based on A1c level
- Titrate to fasting glucose target
 - Increase by 10-15% or 2-4 units once or twice weekly until fasting glucose level attained or total dose 50 units
 - Decrease by 4 units or 10-20% for hypoglycemia

Approach To Starting and Adjusting Insulin in Type 2 Diabetes



Diabetologia 2012;55;1577



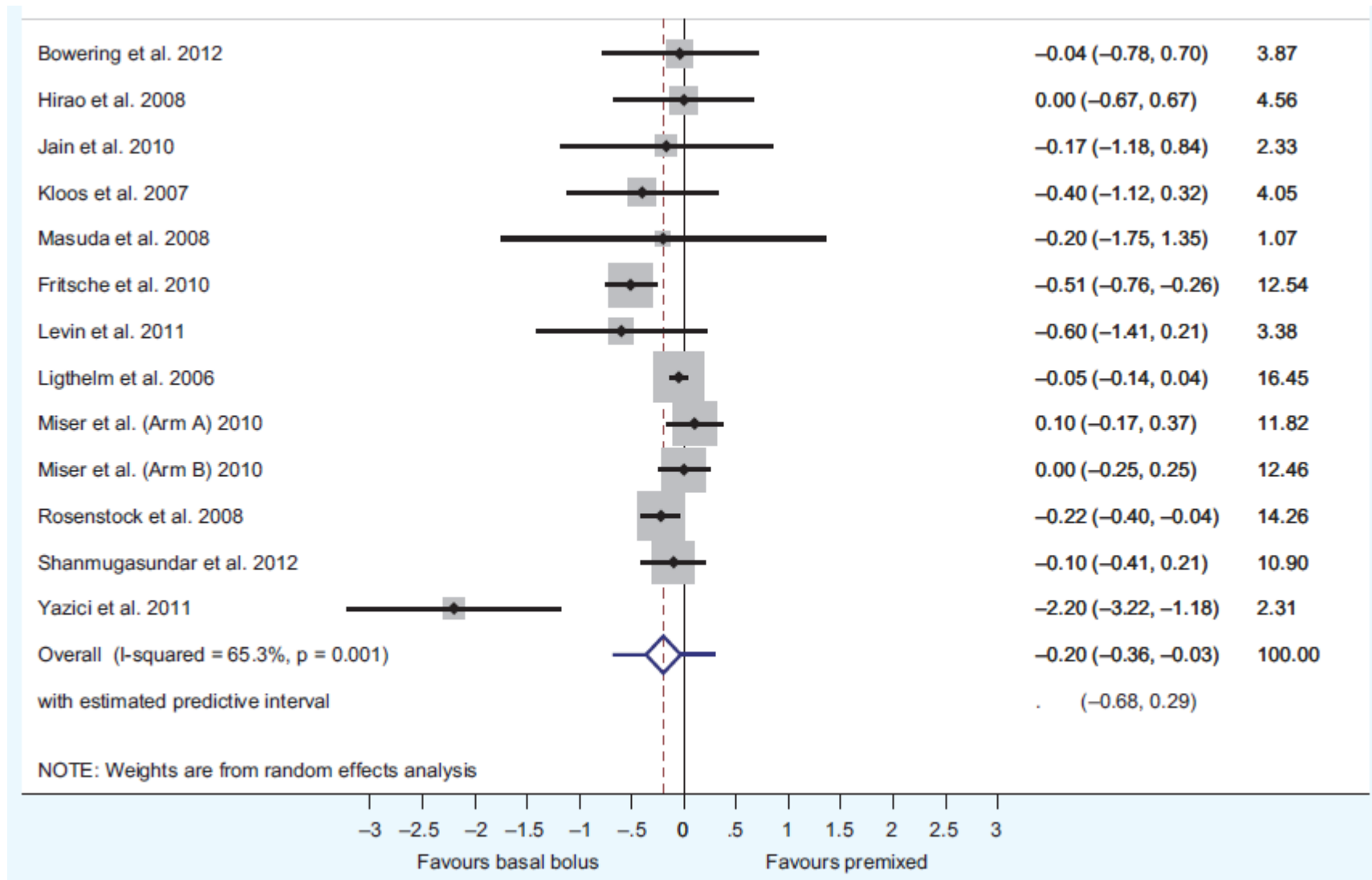
Adding/Intensifying Insulin Algorithm

Endocr Pract 2013;19;327

Beyond Basal Insulin

- If target fasting glucose attained but daytime control suboptimal, or if total daily basal insulin dose is 50 units, consider:
 - *Adding* GLP1 RA (or DPP4-i)
 - *Adding* RAI analog
 - Stop sulfonylurea, continue metformin
 - 10% of basal dose before *largest* meal (A1c < 8%?)
 - 10% of basal dose before *each* meal (A1c > 8%?)
 - Titrate weekly (usually with provider follow-up)
 - *Switching* to biphasic insulin
 - Stop sulfonylurea, continue metformin
 - TDD 2/3 AM, 1/3 PM
 - TDD 1/2 AM, 1/2 PM
 - Titrate weekly (usually with provider follow-up)

Basal Bolus vs. Biphasic Insulin

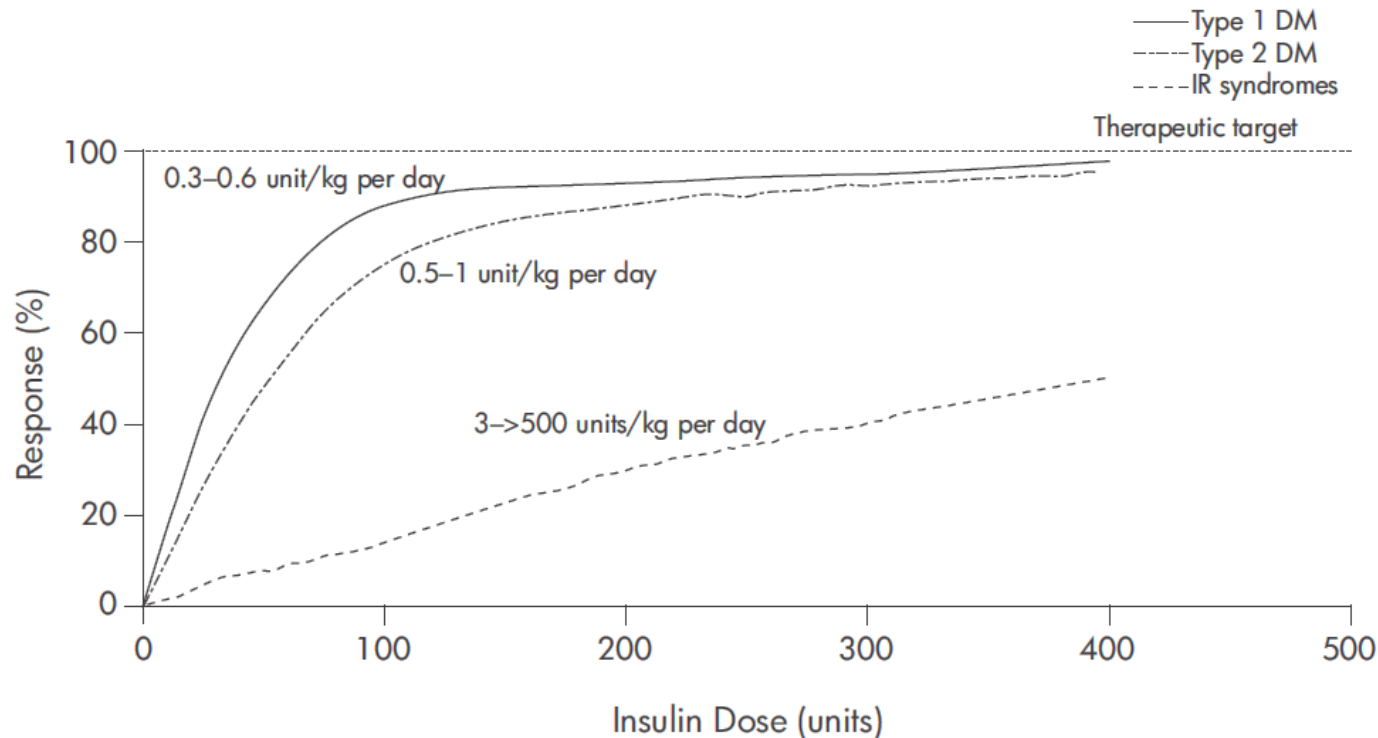


Diabet Med 2015;32;585

Severe Insulin Resistance

- Patients who require more than 200 units of insulin daily are considered to have severe IR
- Large insulin volumes can cause injection site discomfort and the need for multiple injections to deliver a single dose
- Large subcutaneous insulin depot may impede insulin absorption and result in delayed hypoglycemia

Concentrated Regular Insulin



- In type 2 diabetes, the dose response at the target level is markedly attenuated and much higher doses of insulin are required to achieve goals
- With U-500 insulin, not only can larger doses be administered but peaks of concentration and action profile are blunted and the effect of the peak is prolonged, with a duration of action similar to U-100 NPH

Clinical Trials of U-500 Regular Insulin

Study	Subjects (n)	Mean duration (months)	Mean baseline HbA1c (%)	Mean HbA1c reduction (%)	Mean baseline TDD (units)	Mean TDD change (units)	Mean weight change (kg)
Studies using MDI (n = 310)							
Garg <i>et al.</i> (24)	16	24	11.34	3.29	313	-31	6.5
Neal <i>et al.</i> (22)	20	6	9.59	1.76	221	-7	3.2
Wafa <i>et al.</i> (20)	15	12	9.8	2.2	219	116	2.02
Nayyar <i>et al.</i> ^a (21)	81	30	10.0	1.1	311	57	5.1
Davidson <i>et al.</i> ^b (17)	11	26	9.9	2.5	304	99.9	8.16
Dailey <i>et al.</i> ^a (23)	40	12	9.4	1.4	240	97	5.7
Boldo <i>et al.</i> ^b (25)	53	36	10.1	1.5	225	69	6.8
Ziesmer <i>et al.</i> (27)	53	20	9.1	1.0	391	24	2.0
Quinn <i>et al.</i> ^c (26)	21	12	9.51	1.8	297.5	57.5	-0.35
Overall effect ^d (95% CI)				1.59 (1.26–1.92)		51.9 (19.6–84.1)	4.38 (2.35–6.41)

U-500R initiation



HbA1c >10% → Increase TDD by 10%

HbA1c 8–10% → Maintain same TDD

HbA1c <8% → Decrease TDD by 10–20%



TDD 150–300 units	Twice daily injections (60/40) <u>Three daily injections</u> (40/30/30, 45/35/20, 40/40/20, or 33/33/33)
TDD 300–600 units	Three daily injections (as above) <u>Four daily injections (30/30/30/10)</u> CSII (50% as basal infusion and 50% as bolus)
TDD >600 units	Four daily injections (25/25/25/25 or 30/30/30/10) CSII

The “Fair Cost” of Insulin

Feb 1, 2016

Lantus SoloStar Pen	\$ 381	15 ml
Levemir FlexTouch Pen	\$ 412	15 ml
Humalog KwikPen	\$ 472	15 ml
Novolog FlexPen	\$ 466	15 ml
Toujeo SoloStar Pen	\$ 349	4.5 ml
Tresiba FlexTouch Pen	\$ 536	9 ml
U500 R vial	\$ >1500 (?)	20 ml
Novolin R vial	\$ 136	10 ml
Novolin N vial	\$ 135	10 ml
Novolin 70/30 vial	\$ 136	10 ml
<i>Relion/Novolin R vial</i>	<i>\$ 24.88</i>	<i>10 ml</i>
<i>Relion/Novolin N vial</i>	<i>\$ 24.88</i>	<i>10 ml</i>
<i>Relion/Novolin 70/30 vial</i>	<i>\$ 24.88</i>	<i>10 ml</i>

In Summary...

- Insulin therapy is ultimately required in most patients with long-standing type 2 diabetes
- For most, basal insulin is effective initial treatment and dose titration can be successfully accomplished by the properly educated patient
- Glycemic targets must be individualized for all patients with diabetes, particularly in those with long-standing type 2 diabetes and comorbidities, limited self-care capacity and limited resources
- The majority of patients initiated on basal insulin replacement will require additional treatment strategies within a few years
- In patients with severe insulin resistance, use of concentrated regular insulin can improve overall glycemic control
- Insulin is costly